REMARKS

The above-noted amendments are respectfully submitted in response to the official action dated July 25, 2005. Claim 113 has been amended to correct a typographical error therein. With respect to all of these amendments, it is believed that these amendments, and the cancellation of claims 112 and 120, clearly obviate the objections to these claims under §§ 112, 102 and 103. In all respects, the claims now pending in this application are therefore considered to be patentable over the prior art cited by the Examiner, and based upon the above amendments and the following comments, reconsideration and allowance of these claims is respectfully solicited.

Claims 67-99, 103, 114 and 121 have been rejected as being unpatentable over Miranda *et al.* under 35 U.S.C. § 103(a). Miranda *et al.* is said to teach a transdermal including a drug and acrylate polymer and a polysiloxane. From 2% to 96% polyacrylate and from 4% to 98% polysiloxane are said to be disclosed, and the acrylate polymer is at least 50% alkyl acrylate monomer, with butyl acrylate being disclosed. The drug is said to be from 0.3% to 50% of the composition, and selegiline and propranolol are said to be specifically referred to at column 10, line 53, and column 11, line 29, thereof. The Examiner refers to the disclosure of co-solvents including propylene glycol and alcohols, at column 13, lines 43-51, and Table II thereof. The Examiner thus concludes that it would be obvious to have a composition comprising an acrylate to deliver selegiline in view of this reference, and as for the claimed hydrophobic acrylic polymer, Miranda *et al.* is said to teach at least 50% butyl acrylate, which is said to render the polymer hydrophilic, and the polymer is said to meet the limitations of claims 89, 94, 103 and 114, because applicants' two claimed monomers; namely a C_1-C_4 alkyl acrylate and a C_4-C_{12} alkyl

acrylate collapse to one monomer for C_4 because the ranges overlap for C_4, and as the claimed drying temperature is 100°F, propylene glycol is said to have a boiling point exceeding that temperature. This rejection is respectfully traversed in view of the above amendments and arguments and for the reasons set forth hereinafter.

The nature of the invention to which claim 67 is directed is one in which a drug, which is defined in the specification as being highly plasticizing in nature, namely, one which is of low molecular weight and liquid at or about room temperature, is utilized in a transdermal system. As is set forth in detail in the specification, the development of such systems, which are able to demonstrate long-term storage stability, reliable release profiles, high levels of skin permeation, and most importantly, which are easy and economical to manufacture, has continued to present a major challenge. In accordance with the present invention, however, it is now possible to tailor the release rate of the drug and its permeation rate through the skin by dealing with the nature of these drugs themselves. Preferably, and in accordance with this invention, the only solvents used in the production of therapeutic adhesive formulations which include a highly plasticizing drug are relatively high volatility solvents, such as ethanol, which are removed upon drying, as are those solvents found in the adhesive polymers themselves for the prevention of *in situ* crosslinking, and/or to maintain the adhesive in liquid form until their removal. Solvents which remain after drying, specifically those such as propylene glycol mentioned in the specification at page 10, paragraph [0026], are specifically <u>not</u> to be used in the present adhesive formulations. Indeed, claim 67 specifically requires that the system be substantially

free of low volatility solvents which are not driven off during drying of these delivery systems. Claim 67 thus specifically excludes solvents such as propylene glycol, which as the Examiner has correctly pointed out, have boiling points above those specifically claimed or used in these drying systems, such as above 100°F.

Turning to the Miranda *et al.* reference itself, the basic thrust of this patent is to devise a transdermal system by blending polymers which are thus used to affect the drug delivery rate from those transdermal compositions. Indeed, after discussing the prior art modification of delivery rates for monolithic transdermal devices using specific single polymer matrices, or a blend of miscible polymers along with enhancers, co-solvents, and the like, the Miranda *et al.* invention is said to comprise a blend of at least two polymers with different solubility parameters to adjust the drug solubility in the matrix itself. Preferably, these patentees employ a polyacrylate along with a polysiloxane therefor. As for the drugs disclosed in Miranda *et al.*, however, while an extensive list of drugs of various kinds is set forth beginning at the bottom of column 10 thereof, the Examiner's reference to selegiline is not believed to be correct. The portion of the specification referred to does not appear to include a disclosure of selegiline. As for reference to disclosure of propranolol, this disclosure is of no relevance hereto, since propranolol is clearly not a highly plasticizing drug, or one which is of low molecular weight and liquid at or about room temperature as required by claim 67. Indeed, propranolol is a solid drug at room temperature. According to the Merck Index, and as is apparently recognized by the Examiner, it has a melting point of 96°C and is in crystalline form. The

propranolol is mentioned in the present specification in connection with other aspects of the present application, including, for example, the invention set forth in claim 1 hereof. However, it is clearly excluded from and is not mentioned in connection with the highly plasticizing drugs which are the subject of claim 67, as noted, for example, at the end of paragraph [0036] on page 13 of the specification. Thus, the overall disclosure of Miranda *et al.* does not even relate to the problems created by these highly plasticizing drugs, much less to a solution therefor.

Even more significant, however, is the fact that the Examiner has himself referred to the inclusion of co-solvents such as propylene glycol and other alcohols disclosed at column 13 of the Miranda *et al.* reference. Indeed, this portion of the specification refers to nitroglycerine as functioning as a plasticizer and then states that for drugs which are not readily soluble in the polymer system co-solvents can be added such as propylene glycol and the like. The list presented there thus includes a number of such solvents which are excluded from the present claims, such as tocopherol, dipropylene glycol, triacetin and mineral oil, as well as others. There is certainly no teaching to exclude such low volatility solvents which are not driven off during drying from the compositions of the present invention, and thus no suggestion as to how to achieve the significant results obtainable in accordance with this invention, whereby transdermal delivery systems of great efficacy can now be produced while using the highly plasticizing drugs which are the subject of claim 67.

Turning to the other claims which are the subject of this rejection, it is noted that independent claim 76 not only again requires that the drug be of low molecular weight and

liquid at or about room temperature, but in this case requires solvents which "consist essentially of" solvents which volatilize during drying, once again excluding solvents such as propylene glycol, which do not so volatilize, as admitted by the Examiner. Claim 85 includes similar limitations with respect to both the drug component and the substantial freedom from low volatility solvents not driven off during drying of these systems. Claim 91 also includes limitations with respect to both the highly plasticizing nature of the drug itself and in this case requires that the solvent system "consist essentially of" solvents which will volatilize during drying of the transdermal delivery system, again excluding solvents such as propylene glycol.

Turning to claim 94, this claim is directed to another aspect of the present invention in which it has been learned that the specific nature of the acrylic polymeric adhesive used in connection with these systems in which highly plasticizing drug components are employed is of great significance. Most particularly, applicants have stressed throughout the specification the specific claimed combination of from 40% to 90% of a C_4-C_{12} alkyl acrylate along with between about 10% and about 40% by weight of a C_1-C_4 alkyl acrylate hardening monomer therein. It is noted, however, that claim 94 has now been amended to differentiate between the C_4-C_{12} alkyl acrylates and the hardening monomers which are the subject of this combination. It is noted, for example, that in the specification this is clarified by the fact that butyl acrylate is listed as a C_4-C_{12} alkyl acrylate, while the alkyl acrylate hardening monomers of the invention are defined, for example, at page 18, paragraph [0047] as including " methyl acrylate, methyl methacrylate, ethyl acrylate, ethyl methacrylate, hydroxyethyl

acrylate and hydroxypropyl methacrylate," and nowhere in the specification is butyl acrylate defined as a hardening monomer. Claim 94 has thus been clarified in this regard, and it is clear that this claim now requires a combination of two alkyl acrylates, specifically including the alkyl acrylate hardening monomers which are an important extra ingredient in the compositions of the present invention. No such disclosure is included in Miranda *et al.* Furthermore, the Examiner's attempt to rely on the disclosure of butyl acrylate in Miranda *et al.* is now believed to be inapposite.

It is therefore respectfully submitted that all of these claims are clearly patentable over the Miranda *et al.* reference, and indeed over all of the prior art cited by the Examiner, and reconsideration and allowance of these claims is respectfully solicited.

Claims 67-70, 72, 76-79, 81, 85-99, 101-110, and 112-121 have been rejected as being unpatentable over Sablotsky under 35 U.S.C. § 103(a). The Examiner contends that Sablotsky teaches a transdermal system with an acrylic polymer, a synthetic rubber and a crosslinking agent, and at least 50% alkyl acrylate is said to be specified at column 4, lines 20-21, with butyl acetate disclosed therein. Nitroglycerine (a liquid), diltiazem and propranolol are specified as drugs, and melamine formaldehyde resin said to be disclosed as a crosslinker. Again, co-solvents including propylene glycol and alcohols are said to be disclosed at column 7, lines 58-65 thereof. The Examiner concludes that it would thus be obvious to make a composition comprising an acrylate to deliver a drug to achieve the beneficial effect of transdermal delivery in view of Sablotsky. This rejection is respectfully traversed in view of the above amendments and arguments and for the reasons set forth hereinafter.

Sablotsky is believed to be even less relevant than Miranda *et al*. Indeed, Sablotsky does not discuss the issue of plasticization as was the case in Miranda *et al*. In any event, it certainly does not propose a solution to this problem, as Miranda *et al*. failed to do.

Sablotsky itself does mention in its background section that high drug concentrations can reduce adhesion, particularly with a drug serving as a plasticizer or a solvent for the adhesive. This was said to be resolved in the past by incorporating crosslinking agents therein for enhancing shear resistance at the expense of tack and peel adhesion. The invention of Sablotsky, however, is to permit both high and low loading of medicament by using a specific dermal composition which includes a multipolymer of an ethylene/vinyl acetate polymer and an acrylate polymer, a rubber, and a tackifying agent. Various additional optional ingredients are also proposed by Sablotsky. Returning to claim 67, it is certainly clear that Sablotsky does not even recognize the fact that, in systems with hydrophobic adhesive polymers such as acrylates, in which a drug is employed which is of low molecular weight and liquid at about room temperature, to maintain the system substantially free of low volatility solvents which are not driven off during drying of the system is advantageous. Quite to the contrary, the Examiner himself has recognized that this patentee specifically includes such solvents which are excluded from the present claims. The disclosure at column 7 of Sablotsky is, in fact, very similar to that in Miranda *et al*., and includes a similar list of co-solvents, including propylene glycol, which are employed in these systems. One essential element of the present invention, however, is that the system must remain substantially free of the low volatility solvents

such as propylene glycol which are not driven off during the drying process and which are taught by the prior art, including Sablotsky. This same reasoning thus also applies with respect to the limitations of claim 76, which defines a system comprising solvents "consisting essentially of" solvents which volatilize during drying, thus excluding propylene glycol, which does not. Similar arguments apply with respect to claims 85 and 91 for the same reasons. Again, with respect to claim 94, in view of the above-noted amendments to this claim and the specific requirement for the two specific alkyl acrylate components, specifically including the alkyl acrylate hardening monomers of this invention, there is no disclosure of same in Sablotsky. This patent simply describes the various polyacrylates which can be employed in a conventional manner, and does not specify combining the two alkyl acrylate components which are so essential to the nature of the invention defined by claims 94, 103 and 114 hereof. The cancellation of claim 121 clearly obviates the rejection of that claim.

Claims 1-3, 5, 8-10, 12-15, 18-28, 67-70, 72, 73, 76-79, 81, 82, and 103-105 have been rejected as being anticipated by Lhila *et al.* under 35 U.S.C. § 102(b). Lhila is said to teach a transdermal system comprising a pressure-sensitive adhesive and specific reference is said to be made to Gelva 788 therein, which is said to be disclosed in the present specification in Example 15 and Tables 2 and 3 hereof. In addition to the amount of polymer disclosed, 0.5% to 15% of triethanolamine and glycerol or polyalkylene glycol are discussed at column 2, lines 39-52, and propylene glycol is again specified as the active. This rejection is respectfully traversed in view of the above amendments and arguments and for the reasons set forth hereinafter.

The Lhila reference is specifically directed to the use of a particular appetite-suppressant drug known as phenylpropanolamine HCl (*i.e.*, PPA). The Lhila patent is thus concerned with the fact that this particular drug has not been found to easily permeate human skin, and thus has been problematic with respect to potential use in transdermal applications. The invention of Lhila is said to be based upon a finding that PPA may be combined with a carrier adhesive and a combination of permeation enhancers to provide transdermal delivery systems. The adhesive systems are said to be known, and include acrylic pressure-sensitive adhesives, including Gelva 788. The permeation enhancers which are required by this patent include polypropylene glycol and the like. The disclosure of Lhila is quite distant from the overall nature and substance of the presently claimed invention.

Turning to claim 1, this claim requires an active agent in protonated form, a nonaqueous solvent which is capable of dissolving a drug in either its protonated or non-protonated form, and a biocompatible deprotonating agent having the required properties of claim 1. The Examiner points to the fact that the disclosure in Lhila includes the requirement for a pH control additive, such as Trolamine 85NF, which is a triethanolamine product. Triethanolamine is indeed one of the deprotonating agents specified in the present specification. However, this does not render the Lhila reference anticipatory since it does not even disclose the basic concept of claim 1; namely, use of a nonaqueous solvent which can dissolve the pharmaceutically active agent in either its protonated or nonprotonated form along with the biocompatible deprotonating agent itself. This failure is understandable, however, since the invention in Lhila merely claims that the PPA can be mixed with

certain permeation enhancers and pH control additives to assist it in transference through the skin. There is no disclosure in this reference of the specific claimed combination of claim 1, nor of any combination which includes a drug in protonated form, a nonaqueous solvent which can dissolve the drug in both its protonated or nonprotonated form, as well as a biocompatible deprotonating agent itself.

Turning to the claims discussed above, including claim 67, it is even more clear that these claims are patentable over Lhila. Firstly, PPA itself is a solid crystalline drug which has a melting point of between 190°C and 194°C, and which clearly cannot be categorized as a highly plasticizing drug in accordance with the present invention. It certainly does not meet the requirements of claim 67 for a drug of low molecular weight and being a liquid at or about room temperature. However, PPA is the only drug to which the Lhila patent is directed. As for the nature of the adhesive itself, the Examiner, in addition to the general disclosure of acrylic adhesives, has pointed to the use of Gelva 788 in this reference. Referring to Table 2 on page 19 of the present specification, however, it is noted that applicants' invention was indeed set forth, but at this point a number of known commercially available transdermal adhesives were listed, including Gelva 788 and others. However, it was noted in this portion of applicants' specification that the selection of the particular combination including the required alkyl acrylate hardening monomers of the present invention, which <u>are</u> specifically included in the Gelva 753 and Durotak 2852 adhesives, which were found to be effective in accordance with the present invention, was in the context of a comparison to compounds such as Gelva 788, which do <u>not</u> include this adhesive

component, but which include vinyl acetate instead. Referring to the results shown in Table 3, applicants rely on this data as quite unexpectedly showing that the properties of these adhesives vary greatly, thus requiring the crucial presence of an alkyl acrylate hardening monomer of the present invention, which is not included in Gelva 788. Thus, the observations with this product were clearly inadequate, as compared, for example, to the results achieved with compounds such as Gelva 1753 and Durotak 2852, in which no transfer was observed. Thus, far from exemplifying the present invention, the disclosure of Gelva 788 in Lhila, a compound which is not within the claimed compositions of the present invention, clearly exemplifies the insufficiencies of this reference to in any way obviate the presently claimed invention. Once again, Lhila's inclusion of solvents or enhancers, such as polypropylene glycol, again exemplifies the fact that this reference utterly fails to teach or suggest the use of a system which is substantially free of low volatility solvents which are not driven off during drying of these systems. These claims again exclude compounds such as polypropylene glycol, which are required by Lhila. Applicants would reiterate all of their prior contentions with respect to claim 76, as well as claim 103 as amended herein.

Claims 1-9, 11-14, 16-28, 67-84, and 94-121 have been rejected as being unpatentable over Wolter *et al.* under 35 U.S.C. § 103(a). The Examiner contends that Wolter *et al.* teaches a transdermal with an adhesive, a drug or salt, and when the salt is present, an element containing basic groups. Selegiline is said to be disclosed, as is ethyl acetate and glycerol. Durotak 2516, which is said to be disclosed in the applicants' specification at Table 3, is specified at column 5, line 9, and polydimethylaminoethyl methacrylate (Eudragit E) is

disclosed, as is propranolol and verapamil. Ethanol is also disclosed therein. The Examiner thus concludes that it would be obvious to make a composition comprising selegiline and an acrylate polymer to achieve the beneficial effect of transdermal delivery, in view of Wolter *et al.* The claimed acrylate polymer, deprotonating agent, drug and solvent composition is said to be achieved when the drug and solvent of Wolter *et al.* enters the matrix of Durotak 2516 and Eudragit E, and without a showing of criticality, ultimate suitable amounts may be obtained by routine experimentation. This rejection is respectfully traversed in view of the above amendments and arguments and for the reasons set forth hereinafter.

The Wolter reference is directed to pharmaceutical substances which are chemically basic in nature. These include selegiline, as well as propranolol, which are said to be volatile under ambient conditions, but which is clearly not the case with respect to propranolol. As noted above, propranolol is a crystalline solid at room temperature. The invention of Wolter *et al.* is then said to comprise a transdermal patch for these allegedly volatile pharmaceutical ingredients of chemically basic nature comprising a multi-element system of a matrix of pressure-sensitive adhesive which includes a salt or contains basic groups to liberate the free base from its salt. Thus, the product is produced by mixing the physiologically acceptable salt of the active agent and a fluid composition of a pressure-sensitive adhesive with a solvent or diluent, followed by evaporation to produce a matrix of homogeneous substrate in layer or particulate form. The solvent thus appears to be used to dissolve the drug and mix it with the adhesive prior to its removal. A separate second layer is then formed of a deprotonating agent, as well as a solvent and adhesive, and the solvent is then once again removed. Of course, the invention of

claim 1 does not require the two separate layers which are essential to Wolter *et al.* In any event, however, Wolter *et al.* specifically discloses the fact that when a salt of the drug is utilized the ability for it to diffuse may be improved by concomitant use of a conventional solubilizer "such as glycerol, 1,2-propanediol, the monomethyl or monoethyl ether of diethylene glycol, 2-oxtyldodecanol, the laurate, palmitate, stearate or oleate of sorbitol, C_8/C_{10} ethoxylated glycerides, and ethoxylated oleic glycerides." (Col. 2, lns. 54-58.) It is thus clear that, particularly with respect to claims such as claim 67, far from disclosing compositions which are substantially free of low volatility solvents which are not driven off during drying, this patentee requires the incorporation of such solvents into the systems thereof. Similarly, at column 3 of Wolter *et al.*, where the patentee describes his second layer (b), it is once again urged that this composition includes compounds which would not meet the limitations of the present claims, and which thus comprise the very same nonvolatile solvents which are specifically excluded by the language of these claims.

It is further noted that the examples in Wolter *et al.* employ as the acrylic adhesive component materials such as Durotak 2516 (col. 5, ln. 9), yet another commercially available acrylic which does not meet the limitations of these claims, and which applicants have in fact demonstrated in their own specification not to be within the scope of these claims, and not to produce the highly improved results of the present invention.

It is therefore respectfully submitted that all of the claims now pending in this application possess the requisite novelty, utility and unobviousness to warrant their immediate

allowance, and such action is therefore respectfully solicited. If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he telephone applicant's attorney at (908) 654-5000 in order to overcome any further objections which he might have to the allowance of these claims.

Finally, if there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

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Respectfully submitted,

By 

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